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TRANSMITTAL FORM

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Filing Date	November 17, 2000
First Named Inventor	BRIESEWITZ, ROGER
Group Art Unit	1644
Examiner Name	HUYNH, PHUONG NEON
Total Number of Pages in This Submission: 26	Attorney Docket Number: STAN-131

ENCLOSURES (check all that apply)

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- ☒ **Credit Card Payment Form**
- ☐ Amendment / Reply
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  - ☐ Affidavits/declaration(s)
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- ☐ Proprietary Information
- ☐ Status Letter
- ☒ Other Enclosure(s) *(please identify below):*

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Remarks

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT

Signing Attorney/Agent (Reg. No.)	**EDWARD J. BABA, 52,581** **BOZICEVIC, FIELD & FRANCIS, LLP**
Signature	
Date	**June 23, 2006**

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APPELLANT'S BRIEF Address to: Mail Stop Appeal Brief-Patents Commissioner for Patents P.O. Box 1450 Alexandria, VA 22313-1450	Application Number	09/716842
	Confirmation Number	8224
	Attorney Docket No.	STAN-131
	Filing Date	November 17, 2000
	First Named Inventor	BRIESWITZ, ROGER
	Examiner	HUYNH, PHUONG NEON
	Group Art	1644
	Title: *TARGETED BIFUNCTIONAL MOLECULES AND THERAPIES BASED THEREON*	

Sir:

This Brief is filed in support of Appellant's appeal from the Examiner's Rejection dated November 22, 2005. No claims have been allowed and Claims 16-18, 22-26, 30-34, 36, 40-44, 46-50, and 52-56 are pending. Claims 16-18, 22-26, 30-34, 36, 40-44, 46-50, and 52-56 are appealed. A Notice of Appeal was filed on April 24, 2006. As such, this Appeal Brief is timely filed.

The Board of Appeals and Interferences has jurisdiction over this appeal pursuant to 35 U.S.C. §134.

The Commissioner is hereby authorized to charge deposit account number 50-0815, order no. STAN-131 to cover the fee required under 37 C.F.R. §1.17(c) for filing Appellant's brief. In the unlikely event that the fee transmittal or other papers are separated from this document and/or other fees or relief are required, Appellant petitions for such relief, including extensions of time, and authorize the Commissioner to charge any fees under 37 C.F.R. §§ 1.16, 1.17 and 1.21 which may be required by this paper, or to credit any overpayment, to deposit account number 50-0815, order no. STAN-131.

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REAL PARTY IN INTEREST

The inventor named on this patent application assigned his entire rights to the invention to The Board of Trustees of the Leland Stanford Junior University.

RELATED APPEALS AND INTERFERENCES

There are currently no other appeals or interferences known to Appellant, the undersigned Appellant's representative, or the assignee to whom the inventor assigned his rights in the instant case, which would directly affect or be directly affected by, or have a bearing on the Board's decision in the instant appeal.

STATUS OF CLAIMS

The present application was filed on November 17, 2000 with Claims 1-38. During the course of prosecution, Claims 1-15, 19-21, 27-29, 35, and 37-38 were canceled and Claims 40-44, 46-50, and 52-56 have been added. Accordingly, Claims 16-18, 22-26, 30-34, 36, 40-44, 46-50, and 52-56 are pending and stand rejected in the present application, all of which are appealed herein.

STATUS OF AMENDMENTS

Amendments to the claims were filed subsequent to issuance of the Final Rejection on February 21, 2006. For purposes of appeal, the proposed amendments were entered.

SUMMARY OF CLAIMED SUBJECT MATTER

The claimed invention is drawn to methods for directing the biodistribution of a drug that binds to a protein target, wherein the drug is directed to an intracellular space upon administration to a mammalian host. The methods employ a bifunctional molecule having a molecular weight that does not exceed about 5000 daltons consisting of a drug moiety and targeting moiety.

Below is a description of each appealed claim and where support for each can be found in the specification.

Independent Claim 16 claims a method of directing the biodistribution of a drug that binds to a protein target, wherein the drug is directed to an intracellular

space upon administration to a mammalian host (see specification at page 4, lines 9-14). The method comprises administering to the mammalian host an effective amount of a bifunctional molecule having a molecular weight that does not exceed about 5000 daltons consisting of a drug moiety comprising said drug or an active derivative thereof and a targeting moiety to an intracellular biodistribution modulating protein optionally joined by a linking group, wherein the drug moiety binds to a protein target and the targeting moiety is a peptidyl-prolyl isomerase ligand, and wherein the bifunctional molecule has a modulated biodistribution upon administration to said mammalian host as compared to a free drug control (see specification at page 5, lines 1-12 and page 19, lines 1-21); to direct the biodistribution of the drug upon administration to the host to an intracellular space as compared to a free drug control (see specification at page 5, lines 13-15).

Claim 17 depends from Claim 16, wherein the bifunctional molecule exhibits enhanced efficacy upon administration to the mammalian host as compared to a free drug control (see specification at page 5, lines 25-27)..

Claim 18 depends from Claim 16, wherein the bifunctional molecule exhibits reduced toxicity upon administration to the mammalian host as compared to a free drug control (see specification at page 5, lines 25-27).

Claim 22 depends from Claim 16, wherein the bifunctional molecule comprises a linking group (see specification at page 22, lines 20-24).

Claims 23 depends from Claim 16, wherein the bifunctional molecule is administered as a pharmaceutical preparation (see specification at page 29, lines 21-25).

Independent Claim 24 claims a method of targeting a drug to an intracellular site of a mammalian host (see specification at page 4, lines 9-14). The method comprises administering to a mammalian host an effective amount of a bifunctional molecule having a molecular weight that does not exceed about 5000 daltons consisting of a drug moiety and a targeting moiety optionally joined by a linking group, wherein the drug moiety and targeting moiety bind to intracellular proteins and the targeting moiety is a peptidyl-prolyl isomerase ligand, and wherein the bifunctional molecule exhibits a modulated biodistribution upon administration to a mammalian host as compared to a free drug control to target the drug to an

intracellular site of a mammalian host (see specification at page 5, lines 1-12 and page 19, lines 1-21).

Claim 25 depends from Claim 24, wherein the bifunctional molecule comprises a linking group (see specification at page 22, lines 20-24).

Claim 26 depends from Claim 24, wherein the bifunctional molecule does not include a linking group (see specification at page 5, line 1).

Independent Claim 30 claims a method of administering a drug to a host in need of a drug, the improvement comprising administering to the host an effective amount of a bifunctional molecule having a molecular weight that does not exceed about 5000 daltons and consisting of the drug moiety comprising the drug or a derivative thereof covalently linked, either directly or through an optional linking group, to a targeting moiety that binds to an intracellular biodistribution modulating protein, wherein the drug moiety binds to an intracellular protein and the targeting moiety is a peptidyl-prolyl isomerase ligand (see specification at page 5, lines 1-12 page 19, lines 1-21, and page 28 lines 17--22).

Claim 31 depends from Claim 30, wherein the host is a mammalian host (see specification at page 32, lines 26-30).

Claim 32 depends from Claim 31, wherein the mammalian host is human (see specification at page 32, lines 26-30).

Claim 33 depends from Claim 30, wherein the drug is a small molecule (see specification at page 6, lines 16-23).

Claim 34 depends from Claim 30, wherein the targeting moiety binds to an endogenous biodistribution modulating protein (see specification at page 17, lines 16-21).

Claim 36 depends from Claim 34, wherein the endogenous biodistribution modulating protein is an intracellular protein (see specification at page 18, lines 3-6).

Claim 40 depends from Claim 16, wherein the peptidyl-prolyl isomerase ligand is a ligand for an FKBP or cyclophilin (see specification at page 21, lines 3-5).

Claim 41 depends from Claim 16, wherein the peptidyl-prolyl isomerase ligand is a ligand for an FKBP (see specification at page 21, lines 13-15).

Claim 42 depends from Claim 41, wherein the ligand for an FKBP is selected from the group consisting of FK506 and rapamycin (see specification at page 21, lines 21-22).

Claim 43 depends from Claim 16, wherein the peptidyl-prolyl isomerase ligand is a ligand for a cyclophilin (see specification at page 21, lines 13-15).

Claim 44 depends from Claim 43, wherein the ligand for a cyclophilin is a cyclosporin (see specification at page 21, lines 26-30).

Claim 46 depends from Claim 24, wherein the peptidyl-prolyl isomerase ligand is a ligand for an FKBP or cyclophilin (see specification at page 21, lines 3-5).

Claim 47 depends from Claim 24, wherein the peptidyl-prolyl isomerase ligand is a ligand for an FKBP (see specification at page 21, lines 21-22).

Claim 48 depends from Claim 47, wherein the ligand for an FKBP is selected from the group consisting of FK506 and rapamycin (see specification at page 21, lines 13-15).

Claim 49 depends from Claim 24, wherein the peptidyl-prolyl isomerase ligand is a ligand for a cyclophilin (see specification at page 21, lines 13-15).

Claim 50 depends from Claim 49, wherein the ligand for a cyclophilin is a cyclosporin (see specification at page 21, lines 26-30).

Claim 52 depends from Claim 30, wherein the peptidyl-prolyl isomerase ligand is a ligand for an FKBP or cyclophilin (see specification at page 21, lines 3-5).

Claim 53 depends from Claim 30, wherein the peptidyl-prolyl isomerase ligand is a ligand for an FKBP (see specification at page 21, lines 13-15).

Claim 54 depends from Claim 53, wherein the ligand for an FKBP is selected from the group consisting of FK506 and rapamycin (see specification at page 21, lines 21-22).

Claim 55 depends from Claim 30, wherein the peptidyl-prolyl isomerase ligand is a ligand for a cyclophilin (see specification at page 21, lines 13-15).

Claim 56 depends from Claim 55, wherein the ligand for a cyclophilin is a cyclosporin (see specification at page 21, lines 26-30).

GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

I. Claims 16-18, 22-26, 30-34, and 36 stand rejected under 35 U.S.C. §112, first paragraph as lacking enablement.

II. Claims 16-18, 22-26, 30-34, 36, 40-44, 46-50, and 52-56 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Forsgren et al (Cancer Res. 39(12):5155-64 (1979)) in view of WO 95/02684.

ARGUMENT

I. Claims 16-18, 22-26, 30-34, and 36 stand rejected under 35 U.S.C. §112, first paragraph as lacking enablement

In the Advisory Action dated April 4, 2006, the Examiner maintains the rejection of Claims 16-18, 22-26, and 36 under 35 U.S.C. §112, first paragraph as allegedly lacking enablement.

In maintaining the rejection, the Examiner asserts the following:

> The amended claims 16 and 24 still recite the targeting moiety is "peptidyl-prolyl isomerase ligand" for the claimed method. The specification discloses only three peptidyl-prolyl isomerase ligands and they are: FK506, rapamycin, and cyclosporine. Said ligands are linked to a drug for a method of directing the drug to an intracellular space upon administration to a mammalian host. Other than the specific peptidyl-prolyl isomerase ligands conjugated to a drug for the claimed method, there is insufficient guidance as how to make other peptyidyl-prolyl isomerase bifunctional molecules having a molecular weight that does not exceed about 5000 daltons for the claimed method.

The Appellants respectfully disagree. The specification provides ample disclosure of exemplary peptidyl-prolyl isomerase ligands. For example, with respect to the FKBP family of peptidyl-prolyl isomerases, the specification provides the following description regarding suitable ligands:

> A variety of ligands are known that bind to FKBPs and may be used in the subject invention. The ligands should specifically bind to an

> FKBP and have an affinity for the FKBP that is between about 10^{-6} and 10^{-10} M. Of interest are both naturally occurring FKBP ligands, including FK506 and rapamycin. Also of interest are synthetic FKBP ligands, including those described in U.S. Patent Nos.: 5,665,774; 5,622,970; 5,516,797; 5,614,547; and 5,403,833, the disclosures of which are herein incorporated by reference.:

(Page 21, lines 13-25).

In addition, with respect to the cyclophilin family of peptidyl-prolyl isomerases, the specification provides the following description regarding suitable ligands:

> Also of interest in this particular set of preferred embodiments are cyclophilin ligands, where such ligands should specifically bind to cyclophilin with an affinity that is between about 10^{-6} and 10^{-9} M. A variety of ligands that bind to cyclophilins are also known, where such ligands include the naturally occurring cyclosporins, such as cyclosporin A, as well as synthetic derivatives and mimetics thereof, including those described in U.S. Patent Nos.: 5,401,649; 5,318,901; 5,236,899; 5,227,467; 5,214,130; 5,122,511; 5,116,816; 5,089,390; 5,079,341; 5,017,597; 4,940,719; 4,914,188; 4,885,276; 4,798,823; 4,771,122; 4,703,033; 4,554,351; 4,396,542; 4,289,851; 4,288,431; 4,220,61 and 4,210,581, the disclosures of which are herein incorporated by reference.

(Page 21, line 26 through page 22, line 4).

The exemplary peptidyl-prolyl isomerase ligands described in the specification have common characteristics that enable them to be used in the bifunctional molecules of the present invention. Such characteristics include, size, affinity to a specific target present in a host, capability of targeting a protein present in the host at an elevated level, as claimed. Accordingly, the examples are believed to be sufficiently representative of the claimed genus, and show proof-of-concept experiments which support the claimed bifunctional approach and use of peptidyl-prolyl isomerase ligands. In fact, the examples provided in the application are representative of at least three species of ligands in the genus of peptidyl-prolyl isomerase ligands.

Furthermore, the Appellants maintain that the present application provides sufficient disclosure to enable the invention to the full scope of the pending claims. The present specification clearly provides extensive description of the bifunctional molecules employed in the subject methods beginning at page 4 of the specification. This includes a generic description of these molecules, a detailed description of these molecules in terms of formulas, an extensive description of each of the component parts of the molecules, e.g., drug moieties (see pages 6 to 16), targeting moieties (see pages 16 to 21) and linking moieties (see pages 22 to 23). The number, kind and quality of these examples is sufficient to support the claims, particularly as amended.

In addition, a detailed description of how to make the targeted bifunctional molecules is provided at pages 24 to 28 of the specification, where specific guidance is provided on how to make the compounds. Three representative methods of making the compounds are described. Furthermore, page 26 provides even more detail regarding bifunctional molecules of the invention that include a peptidyl-prolyl isomerase-targeting moiety.

Guidance on how to screen candidate bifunctional molecules for suitability of use in the claimed methods is provided on page 25. In addition, page 29 of the specification provides an extensive description on how to use the bifunctional molecules in various applications, including dosages and administration routes, types of hosts, types of conditions, etc. While such screening does involve some experimentation, it is not undue, and is within the reasonable expectation of success of a person of ordinary skill in the art. The basic techniques are well-known, and their application to the present invention is described. Here, there is clear guidance as to the fundamental structural and functional requirements for a bifunctional molecule as claimed, and a reasonable expectation of success.

Therefore, the Appellants maintain that the methods disclosed in the present specification in conjunction with the knowledge available in the art at the time the

present application was filed, would enable one of ordinary skill in the art to practice the invention to the full scope of the pending claims.

In sum, the amount of experimentation required to subject invention would not be undue and excessive because working examples have been provided, guidance is given on how to generate such compounds, and one of skill in the art would be able to perform the experiments as a matter of routine. The specification therefore provides sufficient enablement such that one of ordinary skill in the art would be able to practice the invention without undue experimentation. Accordingly, the specification clearly enables the subject invention as demonstrated in view of the remarks presented herein and in view of the relevant *Wands* factors, as applied in the response filed on December 23, 2004.

II. Claims 16-18, 22-26, 30-34, 36, 40-44, 46-50, and 52-56 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Forsgren et al (Cancer Res. 39(12):5155-64 (1979)) in view of WO 95/02684.

In the Final Office Action, the Examiner maintains the rejection of Claims 16-18, 22-23, 30-34, 36, and 39-56 under 35 U.S.C. §103(a) as allegedly being unpatentable over Forsgren et al. (Cancer Res., 39(12):5155-5164 (1979)), in view of WO 95/02684.

With respect to rejections made under 35 U.S.C. § 103, the MPEP at § 2142 states the following:

> To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. **Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations.** The teaching or suggestion to make the claimed combination and the reasonable expectation of

> success must both be found in the prior art, and not based on applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991) (emphasis added).

It is respectfully submitted that the Examiner's *prima facie* case of obviousness is deficient because the cited prior art fail to teach or suggest all the claim limitations of the rejected claims. Below are the contentions of the Appellants with respect to the grounds of rejection made by the Examiner.

The present claims are directed to methods for directing the biodistribution of a drug that binds to a protein target, wherein the drug is directed to an intracellular space upon administration to a mammalian host, by:

(1) administering to the mammalian host an effective amount of a bifunctional molecule having a molecular weight that does not exceed about 5000 daltons consisting of a **drug moiety optionally joined by a linking group to a peptidyl-prolyl isomerase ligand** targeting moiety, wherein said bifunctional molecule has a modulated biodistribution upon administration to said mammalian host as compared to a free drug control;

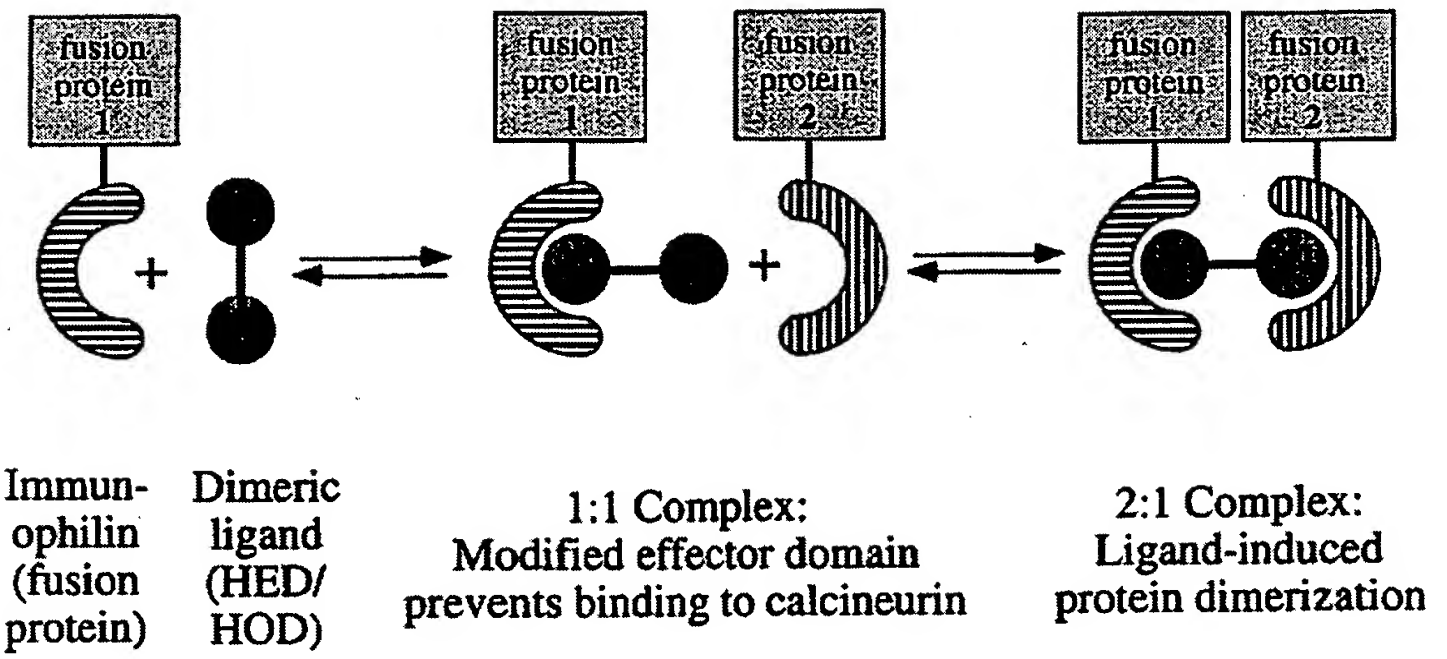
(2) **to direct the biodistribution of the drug upon administration to the host to an intracellular space as compared to a free drug control**.

In maintaining the rejection, the Examiner asserts in the Final Office Action that it would have been obvious "to substitute the estrogen targeting moiety as taught by Forsgren et al for the targeting moiety such as peptidyl-prolyl isomerase ligand FK506 type ligand, cyclosporine and rampamycin...as taught by the WO 95/02684" (Office Action, page 13). However, the Appellants respectfully disagree.

As developed in the analysis below, the Examiner's position is based on the incorrect reading of the recombinant proteins of WO 95/02684. Specifically, the Examiner's position is based on the incorrect assumption that the recombinant proteins include peptidyl-prolyl isomerase ligands.

In particular, the Appellants stress that WO 95/02684 teaches a system that includes two elements: (1) chimeric proteins and (2) ligand molecules capable of oligomerizing the chimeric proteins. According to the cited reference, the chimeric protein includes a ligand-binding (or "receptor") domain fused to an action domain capable of initiating apoptosis (see page 3, lines 24-26). The cited reference further teaches that the receptor domain of such chimeric proteins are "capable of **binding to** FK-506-type ligand, a cyclosporine A-type ligand, tetracycline or a steroid ligand" that are present in a cell and are referred to in the cited reference as oligomerization ligands (see page 4, lines 31-35, emphasis added). Therefore, the cited reference does not teach a moiety such as a peptidyl-prolyl isomerase ligand FK506 type ligand, cyclosporine and rampamycin as a targeting domain of a chimeric molecule, **but instead teaches that such molecules can be targeted, thereby inducing oligomerization in the cell.** In other words, the reference refers to receptors such as FK506, and does not use ligands to those receptors for constructing bifunctional molecules (ligand plus drug) as claimed. Therefore, substitution of the targeting moiety, as taught in WO 95/02684, with the targeting moiety of Forsgren et al., would not result in the claimed bifunctional molecule of the present invention.

As noted on page 14, line 32 of the cited reference, the concept for the inducible protein association is illustrated in Figure 12, reproduced below:



The figure illustrates that the chimeric protein (indicated as the fusion protein) complexes with ligand molecule to form ologomerized complexes of the chimeric protein. The cited reference teaches use of **peptidyl-prolyl isomerase as a receptor domain of the chimeric protein and ligands of peptidyl-prolyl isomerase as inducing ologomerized complexes.**

The Examiner also asserts in the Final Office Action the following:

> "WO 95/02684 publication teaches a bifunctional molecule such as fusion protein comprising **a targeting moiety such as various peptidyl-prolyl isomerase ligand linked to FAS** (see page 14, lines 1-6, in particular) and methods of making the same as a pharmaceutical."

(emphasis added, Office Action, page 15).

However, the Appellants respectfully disagree. The cited passage discloses a chimeric protein comprising FAS linked to the targeting moiety FKBP12. **FKBP12 is a peptidyl-prolyl isomerase – not the ligand of a peptidyl-prolyl isomerase**. The Office Action further notes that the "reference targeting domain such as FK506, cyclosporine and rampamycin is the same targeting domain...as defined by the present specification" (Office Action, page 15).

Again, Appellants respectfully disagree. As previously noted, the disclosure of FK506, cyclosporine and rampamycin in WO 95/02684 is within the context of their use as oligomerizing ligands – not as targeting domains of bifunctional molecules. The cited passage, of the reference specifically states:

> As discussed in greater detail later, and by way of example, in various embodiments of this invention the chimeric protein is capable of binding to an FK506-type ligand, a cyclosporin A-type ligand, tetracycline or a steroid ligand. Such binding leads to oligomerization of the chimeric protein with other chimeric protein molecules which may be the same or different.

(Page 4, lines 31-35).

If, according to the cited passage, the chimeric protein is capable of binding to ligands such as FK506, cyclosporine and rampamycin, then the disclosed chimeric protein **cannot** have such a compound as the targeting domain.

Moreover, the cited reference further provides on page 31, lines 1-3, that such a domain can be a FKBP and a cyclophilin **receptor** – not the ligand of such a receptor, as incorrectly stated in the Office Action. In the context of ologomerizing lands, the cited reference teaches ligands capable of binding to FKBPs (see page 35, line 35-37).

Accordingly, the Appellants maintain that the cited reference does not teach use of ligands of peptidyl-prolyl isomerases as targeting moieties. If, *in arguendo*, one were to combine the teaching of WO 95/02684 with that of Forsgren et al., the result would be a bifunctional molecule having a drug moiety and a targeting moiety that is a **peptidyl-prolyl isomerase**, such as FBKP12. In contrast, the pending claims are directed to a bifunctional molecule having a drug moiety and a targeting moiety that is a **ligand of a peptidyl-prolyl isomerase**. As such, the combination of the two references does not teach using a ligand of a peptidyl-prolyl isomerase as a targeting moiety.

In the Advisory Action dated April 4, 2006, the Examiner asserts the following:

> The WO 95/02684 teaches a peptidyl-prolyl isomerase ligand such as FK506 and cyclosporine that binds to intracellular biodistribution modulating protein such as FKBP12 to form complex such as FKBP12-FK506 complex (see page 35, lines 19-36, page 40, lines 25-40, in particular). The use of the binding partner of FKBP or cyclophilin, in this case, the ligand FK506 and cyclosporine, respectively, as a targeting moiety to target drug is an obvious variation of the reference teachings, especially in light of the teachings of the WO 95/02684 that FK506 interacts with FKBP12 while cyclosporine A interacts with its intracellular receptor cyclophilin (page 40, lines 25-29) and the ligand has a size limitation of less than 5kD (see page 4, line 13, page 33, lines 22-26, in particular).

(Advisory Action, page 2).

However, Appellants respectfully disagree. The disclosure of the cited reference is directed to use of (1) the chimeric proteins and (2) the ligand molecules capable of oligomerizing the chimeric proteins to induce apoptosis of the recipient cells. The cited reference does not teach use of the receptor domains of the chimeric proteins as targeting moieties. In fact, in the context of the disclosure of WO 95/02684, the chimeric proteins and the ligand molecules are both administered to the cells at the same time. Therefore, there is no "targeting" mediated by the receptor domain of the chimeric protein as incorrectly asserted by the Examiner.

As noted above, the claims of the present application require that upon administration to the host, the bifunctional molecule is directed to an intracellular space and results in a directed biodistribution of the dug as compared to a free drug control. The cited reference does not teach or suggest modulating the biodistribution of the disclosed chimeric protein. Therefore, it would be unreasonable to assume that the receptor molecule can be substituted with the ligand molecule in bifunctional molecule, administer the ligand molecule without the receptor, and result in a modulated biodistribution of the bifunctional molecule in a host.

Accordingly, the combination of the references fails to teach each and every limitation found in the claims of the present invention. Therefore, the combination of the cited references cannot render the present application obvious. As such, the Appellants respectfully request that this rejection be withdrawn.

SUMMARY

I. Claims 16-18, 22-26, 30-34, and 36 are enabled under 35 U.S.S § 112, first paragraph, because the specification provides sufficient enablement such that one of ordinary skill in the art would be able to practice the invention without undue experimentation.

II. Claims 16-18, 22-26, 30-34, 36, 40-44, 46-50, and 52-56 are patentable over Forsgren et al (Cancer Res. 39(12):5155-64 (1979)) in view of WO 95/02684 under 35 U.S.C. §103(a) because the references fail to teach or suggest a bifunctional molecule having a peptidyl-prolyl isomerase ligand as a targeting domain and a drug domain that upon administration to the host, the bifunctional molecule is directed to an intracellular space and results in a directed biodistribution of the dug as compared to a free drug control.

RELIEF REQUESTED

The Appellant respectfully requests that the rejections of Claims 16-18, 22-26, 30-34, 36, 40-44, 46-50, and 52-56 under 35 U.S.C. §103(a) be reversed, and that the application be remanded to the Examiner with instructions to issue a Notice of Allowance.

Respectfully submitted,

Date: June 23, 2006

By: _____
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CLAIMS APPENDIX

16. A method for directing the biodistribution of a drug that binds to a protein target, wherein the drug is directed to an intracellular space upon administration to a mammalian host, said method comprising:

administering to said mammalian host an effective amount of a bifunctional molecule having a molecular weight that does not exceed about 5000 daltons consisting of a drug moiety comprising said drug or an active derivative thereof and a targeting moiety to an intracellular biodistribution modulating protein optionally joined by a linking group, wherein said drug moiety binds to a protein target and said targeting moiety is a peptidyl-prolyl isomerase ligand, and wherein said bifunctional molecule has a modulated biodistribution upon administration to said mammalian host as compared to a free drug control;

to direct said biodistribution of said drug upon administration to said host to an intracellular space as compared to a free drug control.

17. The method according to Claim 16, wherein said bifunctional molecule exhibits enhanced efficacy upon administration to said mammalian host as compared to a free drug control.

18. The method according to Claim 16, wherein said bifunctional molecule exhibits reduced toxicity upon administration to said mammalian host as compared to a free drug control.

22. The method according to Claim 16, wherein said bifunctional molecule comprises a linking group.

23. The method according to Claim 16, wherein said bifunctional molecule is administered as a pharmaceutical preparation.

24. A method for targeting a drug to an intracellular site of a mammalian host, said method comprising:

administering to said mammalian host an effective amount of a bifunctional molecule having a molecular weight that does not exceed about 5000 daltons consisting of a drug moiety and a targeting moiety optionally joined by a linking group, wherein said drug moiety and targeting moiety bind to intracellular proteins and said targeting moiety is a peptidyl-prolyl isomerase ligand, and wherein said bifunctional molecule exhibits a modulated biodistribution upon administration to a mammalian host as compared to a free drug control;

to target said drug to an intracellular site of a mammalian host.

25. The method according to Claim 24, wherein said bifunctional molecule comprises a linking group.

26. The method according to Claim 24, wherein said bifunctional molecule does not include a linking group.

30. In a method of administering a drug to a host in need of said drug, the improvement comprising:

administering to said host an effective amount of a bifunctional molecule having a molecular weight that does not exceed about 5000 daltons and consisting of said drug moiety comprising said drug or a derivative thereof covalently linked, either directly or through an optional linking group, to a targeting moiety that binds to an intracellular biodistribution modulating protein, wherein said drug moiety binds to an intracellular protein and said targeting moiety is a peptidyl-prolyl isomerase ligand.

31. The method according to Claim 30, wherein said host is a mammalian host.

32. The method according to Claim 31, wherein said mammalian host is human.

33. The method according to Claim 30, wherein said drug is a small molecule.

34. The method according to Claim 30, wherein said targeting moiety binds to an endogenous biodistribution modulating protein.

36. The method according to Claim 34, wherein said endogenous biodistribution modulating protein is an intracellular protein.

40. The method according to Claim 16, wherein said peptidyl-prolyl isomerase ligand is a ligand for an FKBP or cyclophilin.

41. The method according to Claim 16, wherein said peptidyl-prolyl isomerase ligand is a ligand for an FKBP.

42. The method according to Claim 41, wherein said ligand for an FKBP is selected from the group consisting of FK506 and rapamycin.

43. The method according to Claim 16, wherein said peptidyl-prolyl isomerase ligand is a ligand for a cyclophilin.

44. The method according to Claim 43, wherein said ligand for a cyclophilin is a cyclosporin.

46. The method according to Claim 24, wherein said peptidyl-prolyl isomerase ligand is a ligand for an FKBP or cyclophilin.

47. The method according to Claim 24, wherein said peptidyl-prolyl isomerase ligand is a ligand for an FKBP.

48. The method according to Claim 47, wherein said ligand for an FKBP is selected from the group consisting of FK506 and rapamycin.

49. The method according to Claim 24, wherein said peptidyl-prolyl isomerase ligand is a ligand for a cyclophilin.

50. The method according to Claim 49, wherein said ligand for a cyclophilin is a cyclosporin.

52. The method according to Claim 30, wherein said peptidyl-prolyl isomerase ligand is a ligand for an FKBP or cyclophilin.

53. The method according to Claim 30, wherein said peptidyl-prolyl isomerase ligand is a ligand for an FKBP.

54. The method according to Claim 53, wherein said ligand for an FKBP is selected from the group consisting of FK506 and rapamycin.

55. The method according to Claim 30, wherein said peptidyl-prolyl isomerase ligand is a ligand for a cyclophilin.

56. The method according to Claim 55, wherein said ligand for a cyclophilin is a cyclosporin.

EVIDENCE APPENDIX

No evidence that qualifies under this heading has been submitted during the prosecution of this application, and as such it is left blank.

RELATED PROCEEDINGS APPENDIX

As stated in the *Related Appeals and Interferences* section above, there are no other appeals or interferences known to Appellant, the undersigned Appellant's representative, or the assignee to whom the inventor assigned his rights in the instant case, which would directly affect or be directly affected by, or have a bearing on the Board's decision in the instant appeal. As such this section is left blank.